

UNITED STATES DISTRICT COURT  
DISTRICT OF MASSACHUSETTS

UNITED STATES OF AMERICA,	)	Civil Action No. 10- <u>10865</u> -MLW
	)	
Plaintiff,	)	
	)	
v.	)	
	)	
GENZYME CORPORATION, a corporation,	)	
and HENRI A. TERMEER,	)	
W. BLAIR OKITA, and,	)	
RONALD BRANNING, individuals,	)	
	)	
Defendants.	)	
	)	

**CONSENT DECREE OF PERMANENT INJUNCTION**

Plaintiff, the United States of America, by its undersigned attorneys, having filed a complaint for permanent injunctive relief against Genzyme Corporation ("Genzyme") and Henri A. Termeer, W. Blair Okita, and Ronald Branning (who was hired by Genzyme and assumed his position as Senior Vice President of Global Product Quality in February 2010, after all the investigations described in the Complaint were completed), individuals (collectively, "Defendants"), and Defendants having appeared and having consented to entry of this Decree without contest, without admitting or denying the allegations in the Complaint, and before any testimony has been taken, and the United States of America, having consented to this Decree;

IT IS HEREBY ORDERED, ADJUDGED, AND DECREED as follows:

I. This Court has jurisdiction over the subject matter of this action and personal jurisdiction over all parties to this action pursuant to 28 U.S.C. § 1345 and 21 U.S.C. § 332.

2. The Complaint for Permanent Injunction states a cause of action against Defendants under the Federal Food, Drug, and Cosmetic Act, 21 U.S.C. §§ 301-399a (the “Act”), and alleges:

A. Defendants violate 21 U.S.C. § 331(a) by introducing and causing to be introduced, and delivering and causing to be delivered for introduction, into interstate commerce articles of drug, as defined by 21 U.S.C. § 321(g)(1), that are adulterated, within the meaning of 21 U.S.C. § 351(a)(2)(B), in that they have been manufactured, processed, packed, labeled, held, and distributed in violation of the current good manufacturing practice (“CGMP”) requirements for drugs, *see* 21 C.F.R. pts. 210 and 211;

B. Defendants violate 21 U.S.C. § 331(k) by causing the adulteration, within the meaning of 21 U.S.C. § 351(a)(2)(B), of articles of drug after shipment of one or more of their components in interstate commerce; and

C. Defendants violate 21 U.S.C. § 331(a) by introducing and causing to be introduced, and delivering and causing to be delivered for introduction, into interstate commerce articles of drug that are adulterated, within the meaning of 21 U.S.C. § 351(c), in that their strength differs from, or their purity or quality falls below, that which they purport or are represented to possess.

3. For purposes of this Decree, the following definitions shall apply:

A. “Allston Facility” shall refer to the Genzyme manufacturing facility located at 500 Soldiers Field Road, Allston, Massachusetts;

B. “Drug(s)” shall have the meaning given the term in 21 U.S.C. § 321(g)(1);

C. “Fill/finish manufacturing operations” shall refer to the following manufacturing operations conducted after formulation of the bulk drug substance: sterile filtration, aseptic filling, lyophilization, capping, crimping, and inspection of vials. It shall not include testing of any kind (e.g., finished product, release, and stability testing), labeling, packaging or storage of vials, or storage or distribution of finished drug product; and

D. “Days” shall refer to calendar days unless otherwise stated.

#### INJUNCTIVE PROVISIONS

4. Except as provided in Paragraph 5 of this Decree, Defendants and each and all of their directors, officers, agents, representatives, employees, attorneys, successors, and assigns, and any and all persons in active concert or participation with any of them who receive actual notice of this Decree by personal service or otherwise, are permanently restrained and enjoined under 21 U.S.C. § 332(a) from directly or indirectly manufacturing, processing, packing, labeling, holding, or distributing any drugs, or causing any of the foregoing, at or from the Allston Facility, unless and until:

A. Defendants’ facilities, methods, processes, and controls used to manufacture, process, pack, label, hold, and distribute drugs at or from the Allston Facility are established, operated, and administered in conformity with CGMP, 21 U.S.C. § 351(a)(2)(B), and 21 C.F.R. Parts 210 and 211;

B. Defendants retain, at Genzyme’s expense, an independent person or persons (the “expert”) to inspect the Allston Facility in the manner described below. The expert shall be qualified by background, training, education, and experience to conduct such inspection and shall be without personal or financial ties—other than a consulting agreement with

Genzyme—to Defendants or their immediate families. Defendants shall notify FDA in writing of the identity and qualifications of the expert as soon as they retain such expert. The expert shall commence a comprehensive inspection of the Allston Facility to determine whether the methods, facilities, processes, and controls used to manufacture, process, pack, hold, and distribute drugs will continuously comply with the Act, CGMP, applicable federal regulations relating to the safety, identity, strength, quality, and purity of drugs, and this Decree (hereafter, collectively, “applicable laws and regulations”). In conducting this inspection, the expert shall review all CGMP deviations at the Allston Facility brought to Defendants’ attention in writing since October 2008 by FDA (including, but not limited to, all Forms FDA-483 issued to Genzyme for the Allston Facility), by the expert, or by any other source. If, at any time before the completion of this inspection, Defendants notify FDA in writing that all fill/finish manufacturing operations have ceased at the Allston Facility, any requirement that the expert inspect methods, facilities, processes, equipment, and controls that relate solely to fill/finish manufacturing operations shall cease. The expert’s inspection shall include, at a minimum, an evaluation as to whether:

- (1) Defendants have made comprehensive facility and equipment design enhancements and/or replacements;
- (2) Defendants’ written production and process controls, including, but not limited to, weight checks and visual inspections of vials, are adequate to monitor the output of, and ensure proper performance of, manufacturing processes that may affect the characteristics of bulk drug substances and in-process and finished drug products;
- (3) Defendants’ equipment is appropriately designed for each of its intended uses and is adequately qualified and maintained;

- (4) Defendants' manufacturing processes and systems have been validated;
- (5) Defendants have established a comprehensive, written quality assurance and quality control program ("QA/QC program") for bulk drug substance, in-process, and finished drug manufacturing. At a minimum, the expert shall determine whether the QA/QC program:
  - a. Operates in coordination with, and under appropriate oversight of, Genzyme's corporate QA/QC management;
  - b. Addresses all facets of compliance monitoring and trend analyses, and internal audit procedures, and ensures that Genzyme's Quality Control Unit, as defined by 21 C.F.R. § 210.3(b)(15), is adequately trained and staffed to evaluate CGMP compliance on an ongoing basis to prevent and correct future deviations from CGMP;
  - c. Includes written standard operating procedures ("SOPs") to ensure that Defendants: (i) thoroughly investigate and document in a timely manner any unexplained discrepancy or the failure of a batch of drug product or any of its components to meet any of the product's or component's specifications, including the extension of such investigation to other batches of the same product and other products that may have been associated with the specific failure or discrepancy; and (ii) take required and timely corrective actions for all products that fail to meet specifications;
  - d. Includes SOPs to ensure that the Defendants thoroughly investigate and document in a timely manner any drug complaints, returns, or adverse events, and any associated trends in these product quality deviations and/or problems, and take any needed corrective actions in a timely manner;

e. Includes SOPs to ensure that Genzyme's corporate QA/QC management participates in or monitors the implementation and verification of corrective actions to prevent future occurrences of product quality deviations and that there are procedures to ensure that such written SOPs are continuously followed;

f. Includes SOPs for the change control system to ensure that Defendants adequately qualify equipment and validate processes when changes are implemented. The SOPs shall, at a minimum, require Defendants to document: (i) how the qualification or validation study was conducted, including the test parameters, product characteristics, production equipment, and clear decision points for what constituted acceptable test results; (ii) whether the protocol for the equipment qualification or process validation study was adhered to during execution of the study—and if not, determine what deviations occurred and what effect(s) the deviations had on the results of the study; and (iii) their review of the qualification or validation study results; and

g. Includes procedures to ensure that SOPs are periodically re-evaluated so that they remain in continuous compliance with applicable laws and regulations and reflect Genzyme's current practices, and that these SOPs provide for all facets of compliance with CGMP to be reviewed and controlled by an independent Quality Control Unit;

(6) Defendants have established adequate management controls for the manufacture of drugs. The expert's review shall include, at a minimum, a description of Defendants' current organizational structure and the specific responsibilities of each of Defendants' organizational units that are involved in manufacturing;

(7) Defendants' employee training and qualification practices are adequate, including, but not limited to, employee training and qualification in CGMP, aseptic processing, inspection techniques, and procedures for responding to product quality deviations;

(8) Defendants have implemented a scientifically sound and appropriate system of laboratory controls that, at a minimum, includes specifications, standards, sampling plans, and test procedures necessary to ensure that components, product containers, closures, in-process materials, labeling, bulk drug substances, and finished drug products are in compliance with applicable laws and regulations; and

(9) Defendants have implemented an effective building and facility control system that describes in sufficient detail cleaning and maintenance schedules, methods, equipment, and materials. The expert shall determine whether the system ensures, at a minimum, that: (a) the materials and procedures used to clean and disinfect rooms and equipment in aseptic processing areas are effective to remove microorganisms and extraneous substances, particularly those that are typically isolated in the aseptic processing environment; (b) materials are used in accordance with written procedures; and (c) written procedures are followed and documented;

C. The expert certifies in writing to FDA that: (1) the expert has inspected the Allston Facility and Defendants' methods, facilities, processes, and controls as described in Paragraph 4.B; (2) all CGMP deviations at the Allston Facility brought to Defendants' attention in writing since October 2008 by FDA, the expert, or any other source have been corrected; and (3) Defendants' methods, facilities, processes, and controls used to manufacture, process, pack, label, hold, and distribute drugs at or from the Allston Facility are in compliance with applicable laws and regulations. As part of this certification, the expert shall include a full and complete

written report with the detailed results of the expert's inspection. In making the certification set forth in this subparagraph, the expert may rely on work or actions the expert performed and the expert's certification of the completion of such work or actions under Paragraph 6. In the event that Defendants have notified FDA in writing that all fill/finish manufacturing operations have ceased at the Allston Facility as of the date of this certification, the expert need not certify as to corrections of deviations or as to compliance with applicable laws and regulations that relate solely to such fill/finish manufacturing operations;

D. FDA representatives inspect the Allston Facility to determine whether the requirements of this Decree have been met, and whether Defendants are in conformity with CGMP, the Act, and its implementing regulations; and

E. FDA notifies Defendants in writing that Defendants appear to be in compliance with the requirements set forth in Paragraphs 4.A-C.

#### EXCLUSIONS

5. Notwithstanding the injunctive provisions of Paragraph 4, Defendants may continue the following activities at the Allston Facility:

A. Manufacturing, processing, testing, packing, labeling, holding, and distributing drugs, including bulk drug substances and finished drug products, or causing any of the foregoing, in accordance with written authorization from FDA under this subparagraph. With the signing of this Decree, FDA provides written authorization for Genzyme to manufacture, process, test, pack, label, hold, and distribute (including for export) or cause any of the foregoing at and from the Allston Facility the drugs Cerezyme, Fabrazyme, Myozyme, and Thyrogen, including necessary associated bulk drug substances, drug components, and finished drug



products. FDA authorizes the production of Thyrogen for the United States market only in strict conformance with the conditions and procedures set forth in the protocol attached hereto as Exhibit A ("Thyrogen protocol"), the Dear Healthcare Provider Letter attached hereto as Exhibit B, and the Certificate of Medical Necessity attached hereto as Exhibit C, all incorporated by reference herein. At any time, in its unreviewable discretion, FDA may in writing revoke or expand its authorization to Genzyme under this subparagraph;

B. Receiving drugs at the Allston Facility from other Genzyme facilities and taking specified actions with respect to those drugs in accordance with written authorization from FDA under this subparagraph. With the signing of this Decree, FDA provides written authorization for Genzyme to: (1) label, pack, hold, and distribute at and from the Allston Facility the drugs Elaprase and Aldurazyme; and (2) perform in-process and release testing at the Allston Facility for the drugs Aldurazyme and Lumizyme. At any time, in its discretion, FDA may revoke or expand its authorization to Genzyme under this subparagraph.

C. Manufacturing, processing, packing, testing, labeling, distributing, and holding drugs or causing any of the foregoing solely for the purpose of performing equipment qualification, validating drug manufacturing processes, or conducting method validation or stability studies. Defendants shall maintain in a separate file at the Allston Facility a written log of all lot numbers of drugs manufactured under this provision, and shall promptly make such log available to FDA upon request;

D. Manufacturing, processing, packing, testing, labeling, holding, and distributing investigational drugs or causing any of the foregoing for the sole purpose of conducting clinical trials under investigational new drug applications, provided that Defendants

comply with applicable laws and regulations relating to the manufacture and distribution of investigational products;

E. Manufacturing, processing, packing, testing, labeling, and holding quantities of drugs or causing any of the foregoing that are necessary for the sole purpose of preparing or supporting a new drug application, abbreviated new drug application, biologics license application, or supplement to any of the foregoing, but such products may not be distributed without prior written authorization from FDA; and

F. Manufacturing, processing, packing, testing, holding, labeling, or distributing products or causing any of the foregoing for the sole purpose of conducting non-clinical laboratory studies or other research and testing that does not involve exposure to human research subjects.

#### ADDITIONAL REQUIREMENTS

6. With respect to those drugs that FDA has authorized Defendants to continue manufacturing under Paragraph 5.A, Defendants shall within ten (10) days after the entry of this Decree retain, at Genzyme's expense, an independent person or persons (the "expert") to inspect the Allston Facility in the manner described below. The expert shall be qualified by background, training, education, and experience to conduct such inspection and shall be without personal or financial ties—other than a consulting agreement with Genzyme—to Defendants or their immediate families and may, if Defendants choose, be the same person or persons retained as the expert pursuant to Paragraph 4. In discharging the obligations described in this paragraph, the expert may rely on work or actions performed by the expert under Paragraph 4. Within ten (10)

days after the entry of this Decree, Defendants shall notify FDA in writing of the identity and qualifications of the expert.

A. Within fourteen (14) days after the entry of this Decree, Defendants shall cause the expert to begin a comprehensive inspection to determine whether the methods, facilities, processes, and controls used to manufacture, process, pack, hold, and distribute the drugs authorized under Paragraph 5.A at or from the Allston Facility continuously comply with applicable laws and regulations. This inspection shall be completed no later than one hundred twenty (120) days after the entry of this Decree. In conducting this inspection, the expert shall review all CGMP deviations at the Allston Facility brought to Defendants' attention in writing since October 2008 by FDA (including, but not limited to, all Forms FDA-483 issued to Genzyme for the Allston Facility), by the expert, or by any other source. The expert's inspection shall include, at a minimum, an evaluation of each of the items described in Paragraph 4.B(2)-(9) with respect to the drugs authorized under Paragraph 5.A.

B. Within twenty (20) days of completing the inspection, the expert shall (1) prepare a detailed, written report of the expert's inspection that addresses, at a minimum, each of the matters described in Paragraph 4.B(2)-(9) with respect to the drugs authorized under Paragraph 5.A. and whether the deviations at the Allston Facility brought to Defendants' attention in writing since October 2008 by FDA (including, but not limited to, all Forms FDA-483 issued to Genzyme for the Allston Facility), by the expert, or by any other source have been corrected, and (2) deliver that report contemporaneously to Defendants and FDA.

C. Within forty-five (45) days of receiving the expert's inspection report, Defendants shall submit a written report ("workplan") to FDA detailing the specific actions

Defendants have taken and/or will take to address the expert's observations and bring Defendants' methods, facilities, processes, and controls used for manufacturing, processing, packing, holding, and distributing the drugs authorized under Paragraph 5.A into compliance with applicable laws and regulations. The specific actions in the workplan shall be set forth in numbered steps and, where appropriate, the numbered steps may include subordinate lettered steps. The workplan shall include a timetable with specific dates for completion of each numbered step and may include, where appropriate, interim dates for completion of subordinate lettered steps. The workplan, including its proposed specific actions and timetable, shall be subject to FDA approval. Defendants shall ensure the implementation of the numbered steps in the workplan in accordance with the timetable approved by FDA.

D. As the actions detailed in the workplan are completed, Defendants shall notify the expert in writing, who shall promptly inspect and verify whether those actions have been completed in a manner that complies with applicable laws and regulations to the expert's satisfaction and in accordance with the workplan timetable approved by FDA. If the expert determines that an action has not been completed to the expert's satisfaction, the expert shall promptly notify Defendants in writing. Beginning thirty (30) days after approval of the workplan by FDA, and quarterly thereafter, the expert shall submit to FDA a table that summarizes the expert's findings regarding whether the actions have been completed to the expert's satisfaction and in accordance with the numbered steps in the workplan timetable. FDA may, in its discretion and without prior notice, periodically inspect the Allston Facility and undertake such additional examinations, reviews, and analyses—as provided in Paragraphs 14 and 18—as FDA deems appropriate to verify whether the actions reported to have been completed have in fact

been adequately completed on time. In the event that FDA determines that an action that has been reported to be completed is inadequate, FDA will notify Defendants in writing, and Defendants shall take appropriate action in accordance with a timetable that is subject to approval by FDA.

E. When the expert determines that all of the actions identified in the workplan approved by FDA have been completed to the expert's satisfaction, the expert shall provide Defendants and FDA with a written certification that all of the actions have been completed and that, based on the inspection conducted under Paragraph 6.A and on the satisfactory completion of the actions in the workplan identified under Paragraph 6.C, Defendants' methods, facilities, processes, and controls used to manufacture, process, pack, hold, and distribute the drugs authorized under Paragraph 5.A are and, if properly maintained and implemented by Defendants, will continuously remain in conformity with applicable laws and regulations.

F. Within forty-five (45) days of receiving the expert's certification, FDA may, in its discretion and without prior notice, begin an inspection of the Allston Facility and undertake such additional examinations, reviews, and analyses—as provided in Paragraphs 14 and 18—as FDA deems appropriate to determine whether Defendants' methods, facilities, processes, and controls used for manufacturing, processing, packing, holding, and distributing the drugs authorized under Paragraph 5.A are in conformity with applicable laws and regulations.

G. If FDA determines that Defendants are not operating in conformity with applicable laws and regulations, FDA will notify Defendants of the deficiencies it observed and take any other action FDA deems appropriate (*e.g.*, issuing an order pursuant to Paragraph 15).

Within thirty (30) days of receiving this notification from FDA, Defendants shall submit to FDA a plan describing the actions Defendants propose to take and a timetable for correcting the deficiencies. The timetable and plan shall be subject to FDA approval. Defendants shall promptly correct all deficiencies noted by FDA in accordance with the FDA-approved timetable and plan, and cause the expert consultant to reinspect the conditions relevant to the deficiencies noted by FDA and either (1) certify that the deficiencies have been corrected to ensure that Defendants' methods, facilities, processes, and controls used for manufacturing, processing, packing, holding, and distributing the drugs authorized under Paragraph 5.A are in conformity with applicable laws and regulations, or (2) notify Defendants and FDA in writing that one or more deficiencies remain uncorrected. If one or more deficiencies have not been corrected, Defendants shall correct the deficiencies to the expert's satisfaction, at which point the expert shall issue the certification to Defendants and FDA. Within forty-five (45) days after FDA receives the certification, FDA may reinspect as it deems necessary.

H. If FDA determines that the manufacturing, processing, packing, holding, and distribution of the drugs authorized under Paragraph 5.A appears to be in conformity with applicable laws and regulations, FDA's New England District Office will notify Defendants in writing, as described below in subparagraphs (1) and (2):

(1) If FDA conducts an inspection pursuant to Paragraph 6.F or a re-inspection pursuant to Paragraph 6.G and finds that the manufacturing, processing, packing, holding, and distribution of the drugs authorized under Paragraph 5.A appears to be in conformity with applicable laws and regulations, this notice will be issued within sixty (60) days after completion of such inspection.

(2) If FDA elects not to conduct an inspection pursuant to Paragraph 6.F or a reinspection pursuant to Paragraph 6.G, this notice will be issued within forty-five (45) days after receipt of the expert's certification under Paragraphs 6.E or 6.G.

I. In the event that Defendants notify FDA in writing that all fill/finish manufacturing operations have ceased at the Allston Facility, the obligations in Paragraph 6 that relate solely to fill/finish manufacturing operations shall cease.

7. In the event that Defendants fail, as determined either by the expert or FDA, to satisfactorily complete one or more of the numbered steps in the workplan in accordance with the timetable approved by FDA in the workplan, FDA shall have the sole and unreviewable discretion to order Genzyme to pay the United States Treasury as liquidated damages the sum of fifteen thousand dollars (\$15,000.00) per drug affected by the incomplete numbered step, per business day, until the numbered step is fully implemented and completed to FDA's satisfaction, except that the following payment conditions ("payment conditions") shall apply: if FDA has ordered liquidated damages under this paragraph and the expert subsequently determines that the numbered step(s) at issue has been fully implemented and completed to the expert's satisfaction, then no further payment shall be required unless and until FDA notifies Genzyme that such numbered step is not adequate, in which case payment shall be due for each business day from the date on which the expert issued such certification until FDA notifies Genzyme that such numbered step has been implemented to FDA's satisfaction.

8. Genzyme agrees:

A. To pay the United States Treasury, within fifteen (15) days after entry of this Decree, equitable disgorgement in the amount of one hundred seventy-five million dollars (\$175,000,000.00);

B. In addition, if one or more numbered steps in the workplan described in Paragraph 6 remain inadequately completed as of the date that the last numbered step is scheduled to be completed in the timetable approved by FDA in the workplan, then FDA shall have the sole and unreviewable discretion to order Genzyme to pay to the United States Treasury: (1) liquidated damages in sum of fifteen thousand dollars (\$15,000.00) per bulk drug, per business day for all bulk drugs manufactured and distributed at or from the Allston Facility after that date; and (2) 18.5% of the product revenue generated by the sale of any unit of drug product for which fill/finish manufacturing operations are conducted at the Allston Facility after that date (with "product revenue" for purposes of this Decree being calculated in the same manner as was done in the Revenue Recognition policy on pages 129-30 of Genzyme's 2009 Annual Report on Form 10-K filed with the U.S. Securities and Exchange Commission). Payments under this subparagraph shall continue until the date that all of the numbered steps in the workplan have been adequately completed to FDA's satisfaction, except that the payment conditions described in Paragraph 7 shall apply. In the event that payments become due under this subparagraph, then, as of the timetable date for the last action, no further liquidated damages payments shall be required under Paragraph 7, provided that Genzyme promptly makes the payments required by this subparagraph; and



C. Any amounts due under Paragraph 8.B shall be determined by a Certified Public Accountant retained by Defendants and shall be calculated on a quarterly basis beginning ninety (90) days after FDA issues its order requiring payment under Paragraph 8.B. Defendants shall cause the Certified Public Accountant to send a written determination and explanation to FDA within forty-five (45) days of the end of each quarter, and payments shall be due and owing five (5) days after the date on which the Certified Public Accountant sends the written determination and explanation to FDA.

9. Defendants represent to FDA that, as of the date of the signing of this Decree, Genzyme intends to transfer the fill/finish manufacturing operations for the drugs authorized under Paragraph 5.A currently performed at the Allston Facility to other manufacturing sites (“new sites”), and that such transfer shall not occur until the methods, facilities, processes, and controls used for manufacturing, processing, packing, holding, and distributing drugs at these new sites are in compliance with applicable laws and regulations. FDA reserves the right to inspect the new sites as and when it deems necessary.

A. Domestic Distribution: In the event that Defendants have not provided written notification to FDA that fill/finish manufacturing operations at the Allston Facility for each drug authorized under Paragraph 5.A and manufactured for domestic distribution have ceased within 180 days after the date upon which FDA approves the comparability protocol for that drug, FDA shall have the sole and unreviewable discretion to order Genzyme to pay to the United States Treasury 18.5% of the product revenue generated by the domestic sale of any unit of that drug for which fill/finish manufacturing operations are performed at the Allston Facility after that date until: (1) Defendants have received written notification from FDA pursuant to

Paragraph 4.E or 6.H that Defendants' manufacturing, processing, packing, holding, and distribution of drugs appears to be in conformity with applicable laws and regulations; or (2) fill/finish manufacturing operations at the Allston Facility for that drug have ceased. In the event that payment becomes due for a unit of drug under both this subparagraph and Paragraph 8.B(2), then FDA may, in its unreviewable discretion, order payment under either this subparagraph or Paragraph 8.B(2), but not both paragraphs.

B. Foreign Distribution: In the event that Defendants have not provided written notification to FDA that fill/finish manufacturing operations at the Allston Facility for all drugs authorized under Paragraph 5.A and manufactured for foreign distribution have ceased by August 31, 2011, FDA shall have the sole and unreviewable discretion to order Genzyme to pay to the United States Treasury 18.5% of the product revenue generated by any unit of drug sold within each foreign market for which fill/finish manufacturing operations are performed at the Allston Facility after August 31, 2011, until: (1) Defendants have received written notification from FDA pursuant to Paragraph 4.E or 6.H that Defendants' manufacturing, processing, packing, holding, and distribution of drugs appears to be in conformity with applicable laws and regulations; or (2) fill/finish manufacturing operations at the Allston Facility for that foreign market have ceased. In the event that payment becomes due for a unit of drug under both this subparagraph and Paragraph 8.B(2), then FDA may, in its unreviewable discretion, order payment under either this subparagraph or Paragraph 8.B(2), but not both paragraphs.

C. In the event that Genzyme successfully transfers its fill/finish manufacturing operations from the Allston Facility but later wishes to resume any fill/finish manufacturing operations at the Allston Facility, Genzyme shall not do so until Defendants

receive written permission from FDA. Defendants must also comply with all other applicable laws and regulations relating to the drugs at issue including, but not limited to, the requirements of any new drug application, abbreviated new drug application, biologics license application, or supplement to any of the foregoing, before resuming fill/finish manufacturing operations at the Allston Facility. If Defendants resume any fill/finish manufacturing operations at Allston Facility and have not received written notification from FDA pursuant to Paragraph 4.E or 6.H that Defendants' manufacturing, processing, packing, holding, and distribution of drugs appears to be in conformity with applicable laws and regulations, FDA shall have the sole and unreviewable discretion to order Genzyme to make the disgorgement payments described in Paragraphs 9.A and/or 9.B.

D. Any amounts paid under Paragraph 9 shall be determined by the Certified Public Accountant retained by Defendants and be due in accordance with the procedures described in Paragraph 8.C.

10. The provisions of this paragraph shall apply to those batch production records generated after the date this decree is signed. Except as provided in subparagraph D, with respect to drugs authorized in Paragraph 5.A manufactured at the Allston Facility between the entry of this Decree and the issuance of the notice under Paragraph 6.H:

A. The expert shall, prior to the distribution of each batch, review all in-process, bulk, and finished product batch production records for that batch and prepare and deliver a written report to the Genzyme Senior Vice President of Global Product Quality. (The expert's review of batch production records for those drugs manufactured after the entry of this

Decree may be done concurrently with Defendants' batch record review process.) The expert's report shall include:

- (1) A list of deviations, if any, from written procedures found in the batch production records; an assessment as to whether an adequate investigation was conducted with respect to the deviations, including an explanation of any corrective actions taken with respect to the deviations; an evaluation as to whether such investigations were conducted in a timely manner;
- (2) An assessment as to whether any deviations might have adversely affected the safety, identity, strength, quality, and purity of the batch;
- (3) A list of any deviations and/or problems that QA/QC program personnel failed to note or address during their review of the batch production records for release of the batch; and
- (4) If appropriate, a certification that all deviations observed by the expert have been resolved to the expert's satisfaction or a determination that the batch must be destroyed.

B. Upon a review of the expert's report, the Genzyme Senior Vice President of Global Product Quality shall determine whether the batch should be released for distribution and inform FDA of such determination in writing. If the Genzyme Senior Vice President for Global Product Quality is unavailable, a Genzyme Vice President of Quality shall determine whether the batch should be released and so inform FDA in writing.

C. The Genzyme Senior Vice President for Global Product Quality shall in writing, on a quarterly basis following the date of entry of this Decree, notify the Genzyme Chief Executive Officer as to the results of the batch record review under subparagraphs A and B.

D. With respect to batch records for drugs authorized in Paragraph 5.A that are generated before August 31, 2010, Defendants will continue to follow the Batch Record

Process Interim Control Protocol dated October 19, 2009 (as amended) and the Investigations Protocol dated October 19, 2009 (as amended), except that Defendants must follow the procedures described in subparagraphs A and B for all batch production records relating to fill/finish manufacturing.

11. Within forty-five (45) days after the entry of this Decree, Genzyme shall submit to FDA an inventory and plan for retention or disposition of all in-process, bulk, and finished products that were manufactured at the Allston Facility that are within Genzyme's possession, custody, and control as of the date of entry of this Decree. Defendants shall also propose a schedule showing dates on which the plan will be completed. Defendants' plan and schedule shall be subject to FDA's written approval. This paragraph does not apply to the drugs authorized under Paragraphs 5.A and B.

12. Within seven (7) days after the entry of this Decree and for a period of no less than twelve (12) months after Defendants have complied with either Paragraph 4 or 6 and have received written notification from FDA pursuant to either Paragraph 4.E or 6.H, whichever notification is received last, Genzyme shall assign an individual from or reporting directly to Genzyme's corporate QA/QC management, who is qualified by background, training, education, and experience to perform the functions described in this paragraph, to work on-site in the Allston Facility. This individual shall have full-time responsibility for monitoring whether employees in the Allston Facility are performing their functions appropriately and the Allston Facility is operating in accordance with applicable laws and regulations including, but not limited to, quality assurance and quality control functions. Each quarter, following the date of entry of this Decree, this individual shall provide a written report directly and concurrently to the

Genzyme Senior Vice President of Global Product Quality, the Genzyme Vice President of U.S. Quality Operations, and the Genzyme Senior Director of Quality Assurance for the Allston Facility. Defendants shall ensure that any adverse findings included in the report are promptly and appropriately addressed. In addition, copies of all reports prepared pursuant to the paragraph shall be maintained by Defendants in a separate file at the Allston Facility and shall be made immediately available for FDA inspection upon request.

PERIODIC INSPECTIONS BY THE AUDITOR

13. After Defendants have complied with either Paragraph 4 or 6 and have received written notification from FDA under either Paragraph 4.E or 6.H, whichever notification is received first, Defendants shall retain, at Genzyme's expense, an independent person or persons (the "auditor") to conduct audit inspections of Defendants' manufacturing and quality operations at the Allston Facility. The auditor shall be qualified by background, training, education, and experience to conduct such audit inspections and shall be without personal or financial ties—other than the consulting agreement with Genzyme—to Defendants or their immediate families and may, if Defendants choose, be the same person or persons retained as the expert pursuant to Paragraphs 4 and/or 6. Defendants shall notify FDA in writing as to the identity and qualifications of the auditor as soon as they retain such auditor.

A. After Defendants receive written notification from FDA under either Paragraph 4.E or 6.H, whichever notification is received first, audit inspections under this paragraph shall commence no less frequently than once every six (6) months for a period of one (1) year, and annually thereafter for an additional four (4) year period after Defendants receive

written notification from FDA pursuant to either Paragraph 4.E or 6.H, whichever notification is received last.

B. At the conclusion of each audit inspection, the auditor shall prepare a detailed written audit report ("audit report") analyzing whether Defendants are in compliance with applicable laws and regulations and identifying in detail any deviations therefrom ("audit report observations"). As a part of every audit report, except the first audit report, the auditor shall assess the adequacy of corrective actions taken by Defendants to correct all previous audit report observations. The audit report shall be delivered contemporaneously to Defendants and FDA no later than thirty (30) days after the audit inspection is completed. In addition, copies of all audit reports shall be maintained by Defendants in a separate file at the Allston Facility and shall be made immediately available for FDA inspection upon request.

C. If an audit report contains information indicating that Defendants are not in compliance with applicable laws and regulations, Defendants shall correct those audit report observations within thirty (30) days of receiving the audit report, unless FDA notifies Defendants in writing that a shorter time period is necessary. If, within fifteen (15) days of receiving the audit report, Defendants believe that correction of the audit report observations will take longer than thirty (30) days, Defendants shall submit to FDA in writing a proposed schedule and plan for completing the corrections ("correction schedule") and provide a justification describing why the additional time is necessary. The correction schedule and plan must be reviewed and approved by FDA in writing prior to implementation by Defendants. In no circumstance shall FDA's silence be construed as a substitute for written approval. Defendants shall complete all corrections according to the approved correction schedule and plan.

D. Within thirty (30) days of Defendants receiving an audit report, unless FDA has notified Defendants in writing that a shorter time period is necessary, or within the time period provided in a correction schedule approved by FDA, the auditor shall review the actions taken by Defendants to correct any audit report observations. Within twenty (20) days of the auditor beginning that review, Defendants shall report in writing to FDA the results of the auditor's review and whether the auditor found that each of the audit report observations has been corrected and, if not, which audit report observations remain uncorrected. In the event that Defendants fail, as determined either by the expert or FDA, to correct any audit report observations within thirty (30) days after Defendants receive an audit report, or after a shorter time period imposed in writing by FDA, or after the time period provided in a correction schedule approved by FDA, then FDA shall have the sole and unreviewable discretion to order Genzyme to pay to the United States Treasury as liquidated damages the sum of fifteen thousand dollars (\$15,000.00) per uncorrected observation, per day, until the observation is corrected to FDA's satisfaction, except that the payment conditions described in Paragraph 7 shall apply.

#### GENERAL PROVISIONS

14. Representatives of FDA shall be permitted, without prior notice and as and when FDA deems necessary, to make inspections of the Allston Facility and take any other measures necessary to monitor and ensure continuing compliance with the terms of this Decree. During such inspections, FDA representatives shall be permitted ready access to the Allston Facility including, but not limited to, all buildings, equipment, finished and unfinished materials and products, containers and packaging material therein, labeling, and other promotional material therein; to take photographs and make video recordings; to take samples—without charge to



FDA—of Defendants' finished and unfinished materials and products, containers and packaging material therein, labeling, and other promotional material; and to examine and copy all records relating to the manufacture, processing, packing, labeling, receiving, holding, and distribution of any and all of Defendants' bulk drug substances, components, in-process, and finished drug products, including all records relating to the implementation of the Thyrogen protocol, in order to ensure continuing compliance with applicable laws and regulations. The costs of all such inspections, record reviews, and sample analyses shall be borne by Genzyme at the rates specified in Paragraph 18. The inspections shall be permitted upon presentation of a copy of this Decree and appropriate credentials. The inspection authority granted by this Decree is separate from, and in addition to, the authority granted to FDA to make inspections under the Act, 21 U.S.C. § 374.

15. If, at any time after entry of this Decree, FDA determines, based on the results of an inspection, the analysis of a sample, a report or data prepared or submitted by Defendants, the expert, the auditor, or any other information, that Defendants have failed to comply with any provision of this Decree, have violated applicable laws and regulations, or that additional corrective actions are necessary to achieve compliance with applicable laws and regulations, FDA may, as and when it deems necessary, order Defendants in writing to take appropriate corrective actions, including, but not limited to, the following:

A. Cease all manufacturing, processing, packing, labeling, holding, and/or distributing any or all drugs;

- B. Recall, at Genzyme's expense, any drugs manufactured, processed, packaged, labeled, held, or distributed by Defendants that are adulterated or otherwise in violation of applicable laws and regulations;
- C. Revise, modify, or expand any report(s) or plan(s) prepared pursuant to this Decree;
- D. Submit additional reports or information to FDA;
- E. Issue a safety alert with respect to a drug manufactured, processed, packaged, labeled, held, or distributed by Defendants;
- F. Require that the auditing cycle be extended; and/or
- G. Take any other corrective actions with respect to any drug manufactured, processed, packaged, labeled, held, or distributed by Defendants at or from the Allston Facility as FDA, in its discretion, deems necessary to bring Defendants and Genzyme's drugs into compliance with applicable laws and regulations.

16. The following process and procedures shall apply when FDA issues an order under Paragraph 15, except as provided in subparagraph (D) below:

A. Unless a different time frame is specified by FDA in its order, within ten (10) business days after receiving such order, Defendants shall notify FDA in writing either that:

(1) Defendants are undertaking or have undertaken corrective action, in which event Defendants also shall describe the specific action taken or proposed to be taken and the proposed schedule for completing the action; or

(2) Defendants do not agree with FDA's order. If Defendants notify FDA that they do not agree with FDA's order, Defendants shall explain in writing the basis for their

disagreement. In so doing, Defendants also may propose specific alternative actions and specific time frames for achieving FDA's objectives.

B. If Defendants notify FDA that they do not agree with FDA's order, FDA will review Defendants' notification and thereafter, in writing, affirm, modify, or withdraw its order, as FDA deems appropriate. If FDA affirms or modifies its order, it shall explain the basis for its decision in writing. The written notice of affirmance or modification shall constitute final agency action.

C. If FDA affirms or modifies its order, Defendants shall, upon receipt of FDA's order, immediately implement the order (as modified, if applicable), and if they so choose, bring the matter before this Court on an expedited basis. While seeking Court review, Defendants shall continue to diligently implement FDA's order, unless the Court sets aside, stays, reverses, vacates, or modifies FDA's order. Any review of FDA's decision under this paragraph shall be made in accordance with the terms set forth in Paragraph 26 of this Decree.

D. The process and procedures set forth above in subparagraphs A-C above shall not apply to any order issued pursuant to Paragraph 15 if such order states that, in FDA's judgment, the matter raises significant public health concerns. In such case, the Defendants shall immediately and fully comply with the terms of that order. Should the Defendants seek to challenge any such order, they may petition this Court for relief while they implement FDA's order.

17. Any cessation of operations or other action described in Paragraph 15 shall continue until Defendants receive written notification from FDA that Defendants appear to be in compliance with applicable laws and regulations, and that Defendants may, therefore, resume

operations. Upon Defendants' written request to resume operations, FDA shall determine within forty-five (45) days of receipt of the request whether Defendants appear to be in such compliance and, if so, issue to Defendants a written notification permitting resumption of operations. The costs of FDA supervision, inspections, investigations, analyses, examinations, reviews, sampling, testing, travel time, and subsistence expenses to implement the remedies set forth in this paragraph and Paragraph 15 shall be borne by Defendants at the rates specified in Paragraph 18 of this Decree.

18. Genzyme shall reimburse FDA for all costs of all FDA inspections, investigations, supervision, analyses, examinations, and reviews specified in this Decree or that FDA deems necessary to evaluate Defendants' compliance with this Decree at the prevailing rates in effect at the time the costs are incurred. As of the date that this Decree is signed by the parties, these rates are: \$87.57 per hour and fraction thereof per representative for inspection work; \$104.96 per hour or fraction thereof per representative for analytical or review work; \$0.50 per mile for travel expenses by automobile; government rate or the equivalent for travel by air or other means; and the published government per diem rate or the equivalent for the areas in which the inspections are performed per-day, per-representative for subsistence expenses, where necessary. In the event that the standard rates applicable to FDA supervision of court-ordered compliance are modified, these rates shall be increased or decreased without further order of the Court.

19. After FDA issues a notification pursuant to Paragraph 4.E or 6.H, Genzyme, Henri A. Termeer, W. Blair Okita, and Ronald Branning, and each and all Genzyme's officers, agents, employees, representatives, successors, assigns, and attorneys, and those persons in active concert or participation with any of the Defendants who receive actual notice of this Decree by

personal service or otherwise, shall be permanently enjoined under 21 U.S.C. § 332(a) from directly or indirectly causing to be introduced or delivered into interstate commerce any drug that is adulterated within the meaning of 21 U.S.C. §§ 351(a)(2)(B) or (c), or from causing the adulteration of any drug while such drug product is held for sale after shipment of one or more of its components in interstate commerce. If, and for so long as, an individual Defendant or an employee of Genzyme ceases to be employed by or act on behalf of Genzyme, then that Defendant or employee shall not be subject to the terms of this Decree except as to such individual's act(s) or failure(s) to act under this Decree prior to the time such individual ceased to be employed by or to act on behalf of Genzyme.

20. Within fifteen (15) days after the date of entry of this Decree, Genzyme shall provide a copy of the Decree, by personal service, personal delivery via electronic mail with acknowledgment of receipt, return receipt email, or certified mail (restricted delivery, return receipt requested), to each of its officers, directors, agents, representatives, attorneys, and to those employees and all other persons who are in active concert or participation with Genzyme's CGMP-related operations in the manufacture of drugs at the Allston Facility. Also, within ten (10) days after the date of entry of this Decree, Defendants shall prominently post a copy of this Decree in the employee common area of the Allston Facility so that it is accessible to all employees who are involved in CGMP-related operations. Defendants shall ensure that this Decree remains posted in the employee common area for a period of no less than twenty-four (24) months. If any person begins employment at the Allston Facility in CGMP-related operations at any time subsequent to the periods described above, Defendants shall, within ten (10) days of the commencement of such employment, deliver a copy of this Decree to such

person. Within thirty (30) days after the date of entry of this Decree, Defendants shall provide to the District Director, New England District Office, an affidavit stating the fact and manner of Defendants' compliance with this paragraph and identify the names and positions of all persons receiving copies of the Decree pursuant to the first sentence of this paragraph. Thereafter, within ten (10) days of receiving a request from FDA for any information or documentation that FDA deems necessary to evaluate compliance with this paragraph, Defendants shall provide such information or documentation to FDA.

21. Defendants shall notify FDA at least thirty (30) days before any of the following events occur if the event would affect Defendants' compliance obligations arising out of this Decree: any reorganization, relocation, dissolution, assignment, or sale resulting in the emergence of a successor corporation, the creation or dissolution of subsidiaries, or any other change in Genzyme's legal status.

22. All FDA orders issued under this Decree shall be issued and signed by the District Director of the New England District Office. If Defendants fail to comply with any time frame or provision of this Decree, including any time frame imposed by this Decree, then Genzyme shall pay to the United States Treasury as liquidated damages the sum of fifteen thousand dollars (\$15,000.00) per violation of this Decree and an additional sum of fifteen thousand dollars (\$15,000.00) for each day such violation continues. The remedy in this paragraph shall be in addition to any other remedies available to the United States under this Decree or the law, but shall not apply to Defendants' failure to: (A) satisfactorily complete any actions in the timetable approved by FDA pursuant to Paragraph 6.C, as payment for such failure is governed by Paragraphs 7 and 8 of this Decree; (B) transfer fill/finish manufacturing operations from the

Allston Facility for the drugs authorized under Paragraph 5.A pursuant to Paragraph 9, as payment for such failure is governed by Paragraph 9 of this Decree; or (C) correct any audit report observations in a timely manner, as payment for such failure is governed by Paragraph 13.D of this Decree.

23. All communications required to be sent to FDA under this Decree shall be prominently marked "Decree Correspondence" and sent to the District Director, New England District Office, U.S. Food and Drug Administration, One Montvale Avenue, 4th Floor, Stoneham, MA 02180. All communications required to be sent to Defendants under this Decree shall be addressed to the Chief Executive Officer, Genzyme Corporation, 500 Kendall Street, Cambridge, MA 02142.

24. If any deadline in this Decree falls on a weekend or holiday, the deadline is continued to the next business day.

25. The parties may at any time petition each other in writing to modify any deadline provided herein, and if the parties mutually agree in writing to modify a deadline, such extension may be granted without seeking leave of this Court.

26. Defendants shall abide by the decisions of FDA, and FDA's decisions shall be final. All decisions conferred upon FDA in this Decree shall be vested in FDA's discretion and, if contested, shall be reviewed by this Court under the arbitrary and capricious standard set forth in 5 U.S.C. § 706(2)(A). Review by the Court of any FDA decision rendered pursuant to this Decree shall be based exclusively on the written record before FDA at the time the decision was made. No discovery shall be taken by either party.

27. Should Plaintiff bring, and prevail in, a contempt action to enforce the terms of this Decree, Defendants shall, in addition to other remedies, reimburse the United States for its attorneys' fees, investigational expenses, expert witness fees, travel expenses incurred by attorneys and witnesses, and administrative court costs relating to such contempt proceedings.

28. This Decree resolves only those claims set forth in the Complaint in this action, and does not affect any other civil, criminal, or administrative claims that the government may have or bring in the future against the Defendants herein.

29. Payments of liquidated damages under Paragraphs 7, 8, 13, and 22 shall not exceed fifteen million dollars (\$15,000,000.00) per year.

30. The parties acknowledge that the payment(s) under this Decree are not a fine, penalty, forfeiture, or payment in lieu thereof.

31. If Defendants have maintained at the Allston Facility in a state of continuous compliance with applicable laws and regulations for at least sixty (60) months after satisfying all of their obligations under Paragraph 4 or 6, whichever is satisfied last, Defendants may petition this Court for relief from this Decree, and the United States will not oppose such petition.

32. This Court retains jurisdiction over this action and the parties thereto for the purpose of enforcing and modifying this Decree and for the purpose of granting such additional relief as may be necessary or appropriate.

SO ORDERED, this 9<sup>th</sup> day of November, 2010.

/s/ Mark L. Wolf

UNITED STATES DISTRICT JUDGE



Entry consented to:

For Defendants

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HENRI A. TERMEER  
Individually and on behalf of  
Genzyme Corporation, as its  
President and Chief Executive Officer

---

W. BLAIR OKITA  
Individually

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RONALD BRANNING  
Individually

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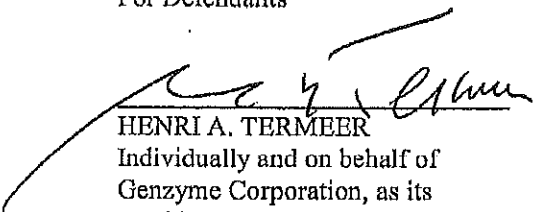
Of Counsel:

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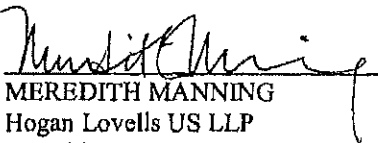
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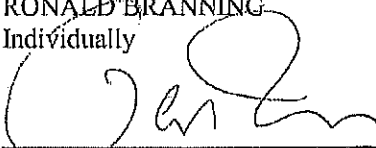
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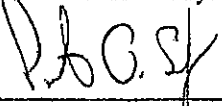
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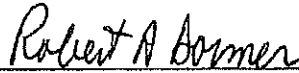
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**Exhibit A****Protocol for the Manufacture and Distribution of Thyrogen**

Genzyme is in the process of transferring its fill/finish manufacturing operations (as provided in the Decree) for Thyrogen from its Allston Facility to other manufacturing sites. Until the transfer is effected, FDA authorizes Genzyme, under Paragraph 5.A of the Decree, to manufacture and distribute Thyrogen at and from the Allston Facility provided that (i) it distributes the drug only to customers (i.e., entities that purchase Thyrogen kits directly from Genzyme in the United States) who execute one copy of the Certificate of Procedures Related to Medical Necessity, and (ii) Genzyme distributes each kit of Thyrogen in the United States with one copy of the Dear Healthcare Provider Letter, which contains FDA's criteria for determining whether Thyrogen is medically necessary for a given patient. The Dear Healthcare Provider Letter and the Certificate of Procedures Related to Medical Necessity are attached to the Decree as Exhibits B and C, respectively.

Genzyme shall not promote the use of Thyrogen by patients in the United States who do not meet the medical necessity criteria as long as fill/finish manufacturing operations for Thyrogen for the United States market continue at the Allston Facility, and failure to abide by this prohibition may result in the imposition of liquidated damages pursuant to Paragraph 22 of the Decree. Shipping Thyrogen to a customer that has executed a Certificate of Procedures Related to Medical Necessity attached as Exhibit C to the Decree shall not constitute promotion, even if physicians prescribe drug from such shipments to patients who do not meet the medical necessity criteria.

1. Procedures for Initiating Fill/Finish Manufacturing Operations for Thyrogen

No later than thirty (30) days prior to a date upon which it intends to conduct fill/finish manufacturing operations for Thyrogen for the U.S. market, Genzyme shall provide written notification to FDA of its intent to conduct such operations ("fill/finish notification"). The fill/finish notification shall be signed by Genzyme's President, Global Manufacturing and shall include, at a minimum, the following information: (1) the current inventory of Thyrogen kits within Genzyme's possession, custody, and control; (2) an estimate for the number of Thyrogen kits needed and the time period in which Genzyme expects to distribute those kits; (3) any other information forming the basis for Genzyme's determination that additional fill/finish manufacturing operations for Thyrogen are necessary to meet demand in the United States; (4) the date(s) of the scheduled fill/finish manufacturing operations; (5) the size of the Thyrogen lot(s) to be produced; and (6) the lot number(s) for the Thyrogen to be produced.

Upon receiving Genzyme's fill/finish notification, and prior to Genzyme's commencement of fill/finish manufacturing operations for Thyrogen, FDA may order Genzyme in writing to (1) revise, modify, expand, or supplement the information contained in the fill/finish notification; (2) suspend or cancel the planned fill/finish manufacturing operations; and/or (3) take any other actions with respect to fill/finish manufacturing operations for Thyrogen that FDA deems appropriate.



2. Recordkeeping and Reporting Requirements for Distribution of Thyrogen

Genzyme shall not distribute Thyrogen manufactured under Paragraph 5.A of the Decree to its customers without first: (a) providing each customer with a copy of the Dear Healthcare Provider Letter regarding Thyrogen, and (b) having the customer execute a single Certificate of Procedures Related to Medical Necessity. Genzyme shall retain in its files copies of the executed Certificate of Procedures Related to Medical Necessity from each customer to which it distributes Thyrogen for so long as the Decree remains in effect. Upon request, Genzyme shall provide copies to FDA of the executed Certificates of Procedures Related to Medical Necessity.

In addition, with each box of Thyrogen drug product destined for the domestic market, Genzyme shall enclose multiple copies of the Dear Healthcare Provider Letter, equal to the number of individual kits of Thyrogen contained in the box. Genzyme shall maintain a record of all orders for, and shipments of, Thyrogen manufactured and distributed under Paragraph 5.A of the Decree, for both domestic and foreign markets, and shall provide such record to FDA upon request.

Each month for the first three months after entry of the Decree, and quarterly thereafter until inventory filled and finished at the Allston Facility for the U.S. market has been depleted, Genzyme shall provide a report to FDA ("distribution report") containing the following information: (1) the inventory of Thyrogen within Genzyme's possession, custody, and control; (2) the names, addresses, and telephone numbers of all customers executing a Certificate of Procedures Related to Medical Necessity for Thyrogen and the dates upon which Genzyme received the forms; (3) the number of kits of Thyrogen shipped to each customer in the time period covered by the report (either monthly or quarterly), the lot numbers of those kits, and the dates of those shipments; and (4) if applicable, the total number of kits shipped to each customer in the year prior to entry of the Decree.

## **Exhibit B**

### **CDER Statement to Healthcare Professionals: Restricted Availability of Thyrogen**

[XX-XX-2010] Healthcare professionals should be aware that the supply of Thyrogen (recombinant thyroid stimulating hormone [TSH]), a drug used in the treatment and follow-up diagnosis of thyroid cancer, will be temporarily limited.

On May \_\_, 2010, the U.S. Food and Drug Administration (FDA) and Genzyme entered into a legal settlement (consent decree) that is designed to permit Genzyme to produce, for the United States market, enough Thyrogen to meet the needs of patients for whom FDA considers the drug to be medically necessary. Accordingly, the consent decree restricts Genzyme's U.S. distribution of Thyrogen to customers (meaning entities that purchase Thyrogen kits directly from Genzyme, such as distributors and wholesalers) who sign a Certificate of Procedures Related to Medical Necessity. This Certificate notes the customer's agreement to distribute the product with this Dear Healthcare Provider Letter, which describes the patients for whom FDA considers Thyrogen to be medically necessary. This restriction will remain in place until Genzyme corrects manufacturing issues at their Allston Landing facility, where the fill/finish manufacturing operations for Thyrogen are performed, or transfers fill/finish manufacturing operations for Thyrogen to other manufacturing facilities operating in compliance with FDA regulations.

The FDA has developed a set of criteria to help healthcare professionals identify patients for whom Thyrogen is considered medically necessary. The following are criteria which should be met for Thyrogen to be considered medically necessary for a patient with thyroid cancer.

1. Patients undergoing initial radioiodine ablation of thyroid tissue remnants, post-thyroidectomy, deemed to be at significantly increased risk of side-effects/complications from undergoing thyroid hormone withdrawal.\*
2. Follow-up testing of patients considered high risk for thyroid cancer recurrence and who have unmeasurable basal thyroglobulin (Tg) levels and are deemed to be at significantly increased risk of side-effects/complications from undergoing thyroid hormone withdrawal.\* The American Thyroid Association's 2009 Guidelines provide a three-level stratification for assessment of risk of thyroid cancer recurrence and identify as "high-risk" those patients who have 1) macroscopic tumor invasion, 2) incomplete tumor resection, 3) distant metastases, and possibly 4) thyroglobulinemia out of proportion to what is seen on the post-treatment scan.

Initial rhTSH stimulation testing in patients not considered high risk for thyroid cancer recurrence may also be considered appropriate if such patients are at risk of side-effects/complications from prolonged hypothyroidism due to thyroid hormone withdrawal.

\*Patients deemed to be at significantly increased risk of side-effects/complications from undergoing thyroid hormone withdrawal for purposes of the two criteria above are:

- Patients with history of stroke, transient ischemic attack, or underlying heart disease, especially heart failure that may be exacerbated by hypothyroidism (NYHA class III or IV)<sup>2</sup>.
- Patients with renal failure (National Kidney Foundation stage  $\geq 3$ )<sup>3</sup> in whom prolonged hypothyroidism will affect clearance of radioactive iodine.
- Patients with a history of or active psychiatric disorders (e.g., depression) that will be exacerbated by hypothyroidism.
- Patients whose overall performance status may be severely compromised during hypothyroidism (e.g., ECOG performance status  $\geq 2$ )<sup>4</sup>.
- Patients on medications with a narrow therapeutic index (e.g., digoxin, lithium, warfarin) for which clearance of medications may be impaired by hypothyroidism.
- Patients with hypopituitarism or who have previously been unable to mount an adequate increase in endogenous thyroid stimulating levels (TSH) levels.
- Patients > 65 years of age regardless of the presence or absence of other concurrent medical conditions.

Generally, pediatric patients are not considered to be within the medically necessary category as they are more likely to tolerate a short period of hypothyroidism and can often mount an adequate elevation of endogenous TSH within two weeks of levothyroxine withdrawal.

**Exhibit C**

&lt;GENZYME LETTERHEAD&gt;

**CERTIFICATE OF PROCEDURES RELATED TO  
MEDICAL NECESSITY FOR THYROGEN**

Dear Customer:

On May \_\_, 2010, Genzyme entered into a Consent Decree of Permanent Injunction with the United States Food and Drug Administration to resolve litigation in which the United States has alleged that Genzyme manufactured, labeled, and distributed drugs at its Allston, Massachusetts facility in violation of the current good manufacturing practice requirements for drugs. Under the terms of the Consent Decree, Thyrogen may be distributed by Genzyme in the United States only to those customers who execute this certification once and agree to ship the product with a copy of the Dear Healthcare Provider Letter provided herewith, which describes the patients for whom Thyrogen is considered medically necessary by FDA. For purposes of this Certificate, "customers" shall mean entities that purchase Thyrogen kits directly from Genzyme. Downstream purchasers who do not purchase directly from Genzyme do not need to execute this certification. In order to receive Thyrogen from Genzyme, customers must execute this Certificate of Procedures Related to Medical Necessity once and return it to Genzyme at:

&lt;Genzyme Mailing Address&gt;

Scan and e-mail to: &lt;email address&gt;

Or fax to: &lt;fax number&gt;

**Required Information**

Customer Name: \_\_\_\_\_ Account #: \_\_\_\_\_

Address: \_\_\_\_\_

City: \_\_\_\_\_ State: \_\_\_\_\_ Postal Code: \_\_\_\_\_

I certify, in my capacity as a representative of the customer identified above, that the customer has received a copy of the Dear Healthcare Provider Letter. I hereby agree that, going forward, with each box of Thyrogen shipped by the customer identified above for use within the United States, the customer will ensure that there are enclosed copies of the Dear Healthcare Provider Letter equal to the number of individual kits of Thyrogen contained in the box.

Authorized Signature: \_\_\_\_\_  
(E.g., Chief Executive Officer, President, Chief Medical Officer, Chief Operating Officer, Hospital Administrator)

Name: \_\_\_\_\_ (please print)

Title: \_\_\_\_\_

Date: \_\_\_\_\_

Telephone number: \_\_\_\_\_ Email address: \_\_\_\_\_